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2		TOX	ICITY CATEGORY PREDICTION	1-2
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4		1.1	Prediction of Toxicity Category by the 3T3 and NHK NRU	
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1.0

19	CATEGORY
20	
21	This analysis of accuracy for the prediction of GHS acute oral toxicity categories (UN 2005)
22	predicted by the 3T3 and NHK NRU test methods was performed using all the available IC_{50}
23	data: 70 substances for the 3T3 NRU and 71 substances for the NHK NRU. Of the 72
24	substances tested in the study, carbon tetrachloride and methanol were excluded from the
25	3T3 NRU analysis and methanol was excluded from the NHK NRU analysis because no
26	laboratory attained sufficient toxicity in any test for the calculation of an IC ₅₀ .
27	
28	1.1 Prediction of Toxicity Category by the 3T3 and NHK NRU Test Methods
29	Using the RC Millimole Regression
30	
31	Table 1-1 shows the concordance of the observed and predicted GHS acute oral toxicity
32	categories (UN 2005) for each in vitro cytotoxicity test method using the geometric mean
33	IC_{50} values (of the three laboratories) in the RC millimole regression, log LD_{50} (mmol/kg) =
34	$0.435 \text{ x} \log \text{IC}_{50} \text{ (mM)} + 0.625$. Accuracy is the agreement of the category predictions with
35	those based on the initial rodent LD_{50} values used for selected substances for testing (in
36	Table 3-2 of the BRD). Substances for which the in vitro toxicity category prediction does
37	not match the in vivo determined toxicity category are considered discordant substances for
38	the GHS toxicity category predictions.
39	
40	For the 3T3 NRU test method, the toxicity category was underpredicted for 29 (56%) and
41	overpredicted for 22 (43%) of the 51 discordant substances. For the NHK NRU test method,
42	toxicity was underpredicted for 28 (54%) and overpredicted for 24 (46%) of the 52
43	discordant substances. The fact that there were more substances that were underpredicted for
44	toxicity is consistent with the RC substances chosen for testing. Figure 3-1 of the BRD
45	shows that most of the selected RC substances are below the RC millimole regression line.
46	Thus, the RC is expected to predict a higher LD ₅₀ (i.e., lower toxicity).

ACCURACY FOR THE PREDICTION OF GHS ACUTE ORAL TOXICITY

Table 1-1 Prediction of GHS Toxicity Category¹ by the 3T3 and NHK NRU Test Methods and the RC Millimole Regression

Initial Rodent		3T3	NRU-Predi	cted Toxicity	 Category		- I		Toxicity	Toxicity
$\mathrm{LD_{50}}^2$	< 5	5 – 50	50 – 300	300 – 2000	2000 - 5000	> 5000	Total	Accuracy	Overpredicted	Underpredicted
< 5	0	3	1	8	0	0	12	0%	0%	100%
5 –50	0	2	5	4	1	0	12	17%	0%	83%
50 – 300	0	0	5	7	0	0	12	42%	0%	58%
300 – 2000	0	0	1	11	0	0	12	92%	8%	0%
2000 - 5000	0	0	0	11	0	0	11 ³	0%	100%	0%
> 5000	0	0	0	7	3	1	11 ⁴	9%	91%	0%
Total	0	5	12	48	4	1	70	27%	31%	41%
Predictivity	0%	40%	42%	23%	0%	100%				
Category Underpredicted	0%	0%	8%	38%	75%	0%				
Category Overpredicted	0%	60%	50%	40%	25%	0%				
Initial Rodent		NHK	NRU-Pred	licted Toxicity	Total	tal Accuracy	Toxicity	Toxicity		
LD_{50}	< 5	5 – 50	50 200	200 2000			i i otai	Accuracy	A 1	Underpredicted
	- 3	5 – 50	50 - 300	300 – 2000	2000 - 5000	> 5000		v	Overpredicted	Onder predicted
< 5	0	1	3	7	2000 – 5000 1	> 5000	12	0%	0%	100%
< 5 5 – 50								,		-
	0	1	3	7	1	0	12	0%	0%	100%
5 – 50	0	1 4	3 7	7	1 0	0	12	0%	0%	100%
5 – 50 50 – 300	0 0 0	1 4 1	3 7 4	7 1 7	1 0 0	0 0 0	12 12 12	0% 33% 33%	0% 0% 8%	100% 67% 58%
5 - 50 50 - 300 300 - 2000	0 0 0 0	1 4 1 0	3 7 4 1	7 1 7 10	1 0 0	0 0 0 0	12 12 12 12	0% 33% 33% 83%	0% 0% 8% 8%	100% 67% 58% 8%
5 - 50 50 - 300 300 - 2000 2000 - 5000	0 0 0 0	1 4 1 0	3 7 4 1 0	7 1 7 10 10	1 0 0 1 1	0 0 0 0	12 12 12 12 12 11 ³	0% 33% 33% 83% 9%	0% 0% 8% 8% 91%	100% 67% 58% 8% 0%
5 - 50 50 - 300 300 - 2000 2000 - 5000 > 5000	0 0 0 0 0	1 4 1 0 0	3 7 4 1 0	7 1 7 10 10 6	1 0 0 1 1 5	0 0 0 0 0	12 12 12 12 12 11 ³ 12	0% 33% 33% 83% 9% 0%	0% 0% 8% 8% 91% 100%	100% 67% 58% 8% 0%
5 - 50 50 - 300 300 - 2000 2000 - 5000 > 5000 Total	0 0 0 0 0 0	1 4 1 0 0 0 0 6	3 7 4 1 0 1 16	7 1 7 10 10 6 41	1 0 0 1 1 5 8	0 0 0 0 0 0	12 12 12 12 12 11 ³ 12	0% 33% 33% 83% 9% 0%	0% 0% 8% 8% 91% 100%	100% 67% 58% 8% 0%

- 49 ¹GHS-Globally Harmonized System of Classification and Labelling of Chemicals with LD₅₀ in mg/kg (UN 2005). The RC
- 50 millimole regression is $\log LD_{50}$ (mmol/kg) = $\log IC_{50}$ (mM) X 0.435 + 0.625. Numbers in table represent number of substances.
- ²Initial rodent LD₅₀ values from Table 3-2 of the BRD.
- ³Carbon tetrachloride excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀.
- 51 52 53 ⁴Methanol excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀.

1.2

Prediction of Toxicity Category by the 3T3 and NHK NRU Test Methods Using 55 the RC Rat-Only Weight Regression 56 57 **Table 1-2** shows the concordance of the observed and predicted GHS acute oral toxicity 58 categories for each test method using the geometric mean IC₅₀ values (of the three laboratories) and the RC rat-only weight regression from Table 6-2 of the BRD. The 59 60 regression formula for the RC rat-only weight regression was $\log LD_{50}$ (mg/kg) = $\log IC_{50}$ 61 (μ g/mL) x 0.372 + 2.024. Accuracy is the agreement of the *in vitro* NRU cytotoxicity GHS toxicity category predictions with those based on the reference rat oral LD₅₀ values from 62 Table 4-2 of the BRD. 63 64 65 The two *in vitro* NRU cytotoxicity test methods over- and under-predicted the GHS toxicity category for a similar number of substances, compared with the GHS toxicity categories for 66 67 the reference LD₅₀ values in Table 4-2 of the BRD. For the 3T3 NRU test method, the GHS 68 toxicity category of 23 (48%) of 48 discordant substances was overpredicted and the GHS 69 toxicity category of 25 (52%) substances was underpredicted. For the NHK NRU test 70 method, the GHS toxicity category of 26 (53%) of 49 discordant substances was 71 overpredicted and the toxicity of 23 (47%) discordant substances was underpredicted. 72

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Table 1-2 Prediction of GHS Toxicity Category¹ by the 3T3 and NHK NRU Test Methods and the RC Rat-Only Weight Regression

			•							
Reference		37	Γ3 NRU Pre	dicted Toxicity	Category				Toxicity	Toxicity
Rodent LD ₅₀ ²	< 5	5 – 50	50 – 300	300-2000	2000-5000	> 5000	Total	Accuracy	Overpredicted	Underpredicted
< 5	0	0	2	5	0	0	7	0%	0%	100%
5 – 50	0	2	5	5	0	0	12	17%	0%	83%
50 - 300	0	0	4	8	0	0	12	33%	0%	67%
300 - 2000	0	1	3	12	0	0	16	75%	25%	0%
2000 - 5000	0	0	0	6	4	0	10^{3}	40%	60%	0%
> 5000	0	0	0	6	7	0	13 ⁴	0%	100%	0%
Total	0	3	14	42	11	0	70	31%	33%	36%
Predictivity	0%	67%	29%	29%	36%	0%				
Category Underpredicted	0%	0%	50%	43%	0%	0%				
Category Overpredicted	0%	33%	21%	29%	64%	0%				
Reference		NE	IK NRU Pro	edicted Toxicity	y Category				Toxicity	Toxicity
Reference Rodent LD ₅₀ ²	< 5	5 – 50	50 – 300	300 – 2000	2000 – 5000	> 5000	Total Accuracy	Overpredicted	Underpredicted	
< 5	0	1	2	4	0	0	7	0%	0%	100%
5 – 50	0	2	5	5	0	0	12	17%	0%	83%
50 – 300	0	1	5	6	0	0	12	42%	8%	50%
300 - 2000	0	1	2	13	0	0	16	81%	19%	0%
2000 - 5000	0	0	0	9	1	0	10^{3}	10%	90%	0%
> 5000	0	0	0	7	6	1	14	7%	93%	0%
				,						
Total	0	5	14	44	7	1	71	31%	37%	32%
	0			,		1 0%	71	31%		32%
Total		5	14	44	7	1 0% 0%	71	31%		32%

¹Globally Harmonized System of Classification and Labelling of Chemicals with LD₅₀ in mg/kg (UN 2005). The RC rat-only weight regression is $\log LD_{50}$ (mg/kg) = $\log IC_{50}$ (µg/mL) X 0.372 + 2.024.

- 77 78 79 80
- 2 Reference rodent LD₅₀ values from Table 4-2 of the BRD. 5 Carbon tetrachloride excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀.
- ⁶Methanol excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀,

81	1.3 Prediction of Toxicity Category by the 3T3 and NHK NRU Test Methods with
82	the RC Rat-Only Weight Regression Excluding Substances with Specific
83	Mechanisms of Toxicity
84	
85	Table 1-3 shows the concordance of the observed and predicted GHS acute oral toxicity
86	categories for each in vitro NRU test method using the geometric mean IC50 values (of the
87	three laboratories) and the RC rat-only weight regression excluding substances with specific
88	mechanisms of action (see Table 6-2). The formula for this regression was log LD_{50} (mg/kg)
89	= log IC ₅₀ (μ g/mL) x 0.357 + 2.194. Accuracy is the agreement of the <i>in vitro</i> predicted
90	GHS toxicity categories with those based on the reference rat oral LD ₅₀ values from Table 4-
91	2 of the BRD.
92	
93	The NHK NRU test method had four more discordant substances than the corresponding
94	assay using $3T3$ cells when the IC_{50} results were applied to the RC rat-only weight regression
95	excluding substances with specific mechanisms of toxicity. For the 3T3 NRU test method,
96	the GHS toxicity category of 16 (38%) of 42 discordant substances was overpredicted while
97	the toxicity of 26 (62%) of 42 discordant substances was underpredicted compared with the
98	in vivo GHS toxicity categories for the reference LD ₅₀ values in Table 4-2 of the BRD. For
99	the NHK NRU test method, the toxicity of 21 (46%) of 46 discordant substances was
100	overpredicted while the toxicity of 25 (53%) of 46 discordant substances was underpredicted.
101	
102	
103	
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Table 1-3 Prediction of GHS Toxicity Categories¹ by the 3T3 and NHK NRU with the RC Rat-Only Weight Regression Excluding Substances with Specific Mechanisms of Toxicity

		20	C2 NIDII D	1°.4.1 T. 1.24	C -1					T. •••
Reference		31	3 NKU Pre	dicted Toxicity	Category		Total	Accuracy	Toxicity	Toxicity Underpredicte
Rodent LD ₅₀ ²	< 5	5 – 50	50 – 300	300-2000	2000-5000	> 5000	Total	Accuracy	Overpredicted	d
< 5	0	0	2	5	0	0	7	0%	0%	100%
5 – 50	0	2	4	6	0	0	12	17%	0%	83%
50 - 300	0	0	3	9	0	0	12	25%	0%	75%
300 - 2000	0	1	1	14	0	0	16	88%	13%	0%
2000 - 5000	0	0	0	4	6	0	10^{3}	60%	40%	0%
> 5000	0	0	0	6	4	3	13 ⁴	23%	77%	0%
Total	0	3	10	44	10	3	70	40%	23%	37%
Predictivity	0%	67%	30%	32%	60%	0%				
Category Underpredicted	0%	0%	60%	45%	0%	0%				
Category Overpredicted	0%	33%	10%	23%	40%	0%				
Deference		NE	IK NRII Pre	edicted Toxicity	v Category			Tovioity	Toxicity	
Reference Rodent LD ₅₀ ²		111		dicted I oxicit,	y Category				Tovicity	TOXICITY
	< 5	5 – 50	50 – 300	300 – 2000	2000 – 5000	> 5000	Total	Accuracy	Toxicity Overpredicted	Underpredicte d
	< 5					> 5000	Total	Accuracy 0%		Underpredicte
Rodent LD ₅₀ ²		5 – 50	50 – 300	300 – 2000	2000 – 5000			·	Overpredicted	Underpredicte d
Rodent LD ₅₀ ² < 5	0	5-50	50 – 300	300 – 2000 5	2000 – 5000	0	7	0%	Overpredicted 0%	Underpredicte d 100%
<pre></pre>	0	5-50	50 – 300 2 5	300 – 2000 5 5	2000 - 5000 0	0	7 12	0%	Overpredicted 0% 0%	Underpredicte d 100% 83%
<pre></pre>	0 0	5-50	50 – 300 2 5	300 – 2000 5 5 7	2000 - 5000 0	0 0	7 12 12	0% 17% 33%	0% 0% 0% 8%	Underpredicte d 100% 83% 58%
<pre>Rodent LD₅₀²</pre>	0 0 0	5-50 0 2 1	50 – 300 2 5 4	300 – 2000 5 5 7 13	2000 - 5000 0 0 0 1	0 0 0	7 12 12 16	0% 17% 33% 81%	0% 0% 8% 13%	Underpredicte d 100% 83% 58% 6%
<pre></pre>	0 0 0 0	5-50 0 2 1 1 0	50 - 300 2 5 4 1 0	300 – 2000 5 5 7 13 6	2000 - 5000 0 0 0 1 4	0 0 0 0	7 12 12 16 10 ³	0% 17% 33% 81% 40%	0% 0% 8% 13% 60%	Underpredicte d 100% 83% 58% 6% 0%
<pre></pre>	0 0 0 0 0	5-50 0 2 1 1 0 0	50 - 300 2 5 4 1 0	300 – 2000 5 5 7 13 6 5	2000 - 5000 0 0 0 1 4 7	0 0 0 0 0	7 12 12 16 10 ³ 14	0% 17% 33% 81% 40% 14%	0% 0% 8% 13% 60% 86%	Underpredicte d 100% 83% 58% 6% 0% 0%
Rodent LD ₅₀ ²	0 0 0 0 0 0	5-50 0 2 1 1 0 0 4	50 - 300 2 5 4 1 0 0 12	300 – 2000 5 5 7 13 6 5 41	2000 - 5000 0 0 1 4 7 12	0 0 0 0 0 2 2	7 12 12 16 10 ³ 14	0% 17% 33% 81% 40% 14%	0% 0% 8% 13% 60% 86%	Underpredicte d 100% 83% 58% 6% 0% 0%

107	Globally Harmonized System of Classification and Labelling of Chemicals with LD ₅₀ in mg/kg (UN 2005). The RC rat-only
108	weight regression excluding substances with specific mechanisms of toxicity is $\log LD_{50}$ (mg/kg) = $\log IC_{50}$ (µg/mL) X 0.357 +
109	2.194.
440	1

- ²Reference rodent LD₅₀ values from Table 4-2 of the BRD.
- 110 111 ⁵Carbon tetrachloride excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀.
- 112 ⁶Methanol excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀,
- 113 114

1.4 Summary of the Regressions Evaluated

Table 1-4 summarizes the regressions evaluated for accuracy in predicting the GHS acute oral toxicity categories (UN 2005), and the proportion of *in vitro* predicted discordant substances for each GHS toxicity category. Accuracy for both NRU cytotoxicity test methods was the same (27% for the RC, 31% for the RC rat-only) for the regressions evaluated except for the RC rat-only weight regression excluding substances with specific mechanisms of toxicity. For the latter regression, the accuracy of the 3T3 NRU test method was higher than that for the NHK NRU (40% vs. 35%, respectively). The proportion of discordant substances for the 3T3 NRU test method was also the same as that for the NHK NRU test method for the RC (73%) and RC rat-only (69%) regressions. The 3T3 NRU had a lower proportion of discordant substances for the RC rat-only weight regression excluding substances with specific mechanisms of toxicity (60% for the 3T3 NRU vs. 65% for the NHK NRU).

Table 1-4 Comparison of Regressions and *In Vitro* NRU Test Methods for Performance in Predicting GHS^a Toxicity Categories

Regression	N ^b	Adjusted R ²	Accuracy	Discordant Substances ^c
RC –millimole units	347	0.450 ^d	3T3 – 27% NHK – 27%	3T3- 51/70 (73%) NHK - 52/71 (73%)
RC rat only –weight units ^e	282	0.322	3T3 – 31% NHK – 31%	3T3- 48/70 (69%) NHK - 49/71 (69%)
RC rat only excluding substances with specific mechanisms of action – weight units ^e	232	0.353	3T3 – 40% NHK – 35%	3T3- 42/70 (60%) NHK – 46/71 (65%)

^aGlobally Harmonized System of Classification and Labelling of Chemicals with LD₅₀ in mg/kg (UN 2005).

The highest accuracy for both *in vitro* NRU cytotoxicity test methods was attained when using the RC rat only weight regression excluding substances with specific mechanisms of action. The accuracy for the 3T3 NRU test method was 40%, which was greater than the accuracy of the 3T3 NRU with the RC millimole regression (27%) and with the RC rat-only weight regression (31%). The accuracy for the NHK NRU test method was 35% for the RC

¹³³ bNumber of substances used in regression.

^{134 &}lt;sup>c</sup>Proportion of substances evaluated.

dCalculated from RC data (i.e., not reported by Halle [1998]).

^eFrom Table 6-1 of the BRD.

144 rat-only weight regression excluding substances with specific mechanisms of toxicity, 27% 145 with the RC millimole regression, and 31% with the RC rat-only weight regression. 146 147 1.5 Alternate Accuracy Analysis for the RC Millimole Regression 148 149 This analysis of accuracy for the prediction of GHS acute oral toxicity categories (UN 2005) 150 by the 3T3 and NHK NRU test methods was performed using the same IC₅₀ data as used for 151 the analyses above (70 substances for the 3T3 NRU and 71 substances for the NHK NRU). 152 However, the *in vivo* GHS categories for this analysis are based on the reference LD₅₀ values 153 presented in Table 4-2 of the BRD rather than the initial LD₅₀ values used to select the 154 substances for testing (in Table 3-2). The analyses presented in **Table 1-1** used the initial 155 LD₅₀ values to determine the *in vivo* GHS acute oral toxicity categories. 156 157 For the 3T3 NRU test method, the toxicity category was underpredicted for 24 (49%) and 158 overpredicted for 25 (51%) of the 49 discordant substances. For the NHK NRU test method, 159 toxicity was underpredicted for 22 (44%) and overpredicted for 28 (56%) of the 50 160 discordant substances.

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Table 1-5 Prediction of GHS Toxicity Category¹ by the 3T3 and NHK NRU Test Methods and the RC Millimole Regression Using Reference LD₅₀ Values for *In Vivo* GHS Categories

	KC MIIII	moic ixc	gi cosioni c	ging recter c	ence LD ₅₀ Val	lucs for A	in rivo	OHS Cate	guiles	
Reference		3T3	NRU-Predi	icted Toxicity	Category		Total	Accuracy	Toxicity	Toxicity
Rodent LD ₅₀ ²	< 5	5 – 50	50 – 300	300 – 2000	2000 - 5000	> 5000	Total	Accuracy	Overpredicted	Underpredicted
< 5	0	2	0	5	0	0	7	0%	0%	100%
5 –50	0	2	5	4	1	0	12	17%	0%	83%
50 – 300	0	0	5	7	0	0	12	42%	0%	58%
300 – 2000	0	1	2	13	0	0	16	81%	19%	0%
2000 - 5000	0	0	0	10	0	0	10^{3}	0%	100%	0%
> 5000	0	0	0	9	3	1	13 ⁴	8%	92%	0%
Total	0	5	12	48	4	1	70	30%	36%	34%
Predictivity	0%	40%	42%	27%	0%	100%				
Category Underpredicted	0%	40%	42%	33%	25%	0%				
Category Overpredicted	0%	20%	17%	40%	75%	0%				
Reference		NHK NRU-Predicted Toxicity Category							Toxicity Toxicity	
Rodent LD ₅₀	< 5	5 50	50 200	200 2000			i i otai	Total Accuracy		TT . J J . 4 . J
	` 3	5 – 50	50 - 300	300 – 2000	2000 - 5000	> 5000		v	Overpredicted	Underpredicted
< 5	0	1	2	4	2000 – 5000 0	> 5000	7	0%	Overpredicted 0%	100%
< 5 5 – 50		1 3								•
	0	1	2	4	0	0	7	0%	0%	100%
5 – 50	0	1 3	2 5	4 3	0	0	7	0% 25%	0%	100%
5 – 50 50 – 300	0 0 0	1 3	2 5 6	4 3 5	0 1 0	0 0 0	7 12 12	0% 25% 50%	0% 0% 8%	100% 75% 42%
5 - 50 50 - 300 300 - 2000	0 0 0 0	1 3 1 1	2 5 6 2	4 3 5 12	0 1 0 1	0 0 0 0	7 12 12 16	0% 25% 50% 75%	0% 0% 8% 19%	100% 75% 42% 6%
5 - 50 50 - 300 300 - 2000 2000 - 5000	0 0 0 0	1 3 1 1 0	2 5 6 2 0	4 3 5 12 10	0 1 0 1	0 0 0 0	7 12 12 16 10 ³	0% 25% 50% 75% 0%	0% 0% 8% 19% 100%	100% 75% 42% 6% 0%
5-50 $50-300$ $300-2000$ $2000-5000$ >5000	0 0 0 0 0	1 3 1 1 0	2 5 6 2 0	4 3 5 12 10 7	0 1 0 1 0 6	0 0 0 0 0	7 12 12 16 10 ³ 14	0% 25% 50% 75% 0%	0% 0% 8% 19% 100%	100% 75% 42% 6% 0%
5-50 50-300 300-2000 2000-5000 > 5000 Total	0 0 0 0 0 0	1 3 1 1 0 0	2 5 6 2 0 1 16	4 3 5 12 10 7 41	0 1 0 1 0 6 8	0 0 0 0 0 0	7 12 12 16 10 ³ 14	0% 25% 50% 75% 0%	0% 0% 8% 19% 100%	100% 75% 42% 6% 0%

- ¹GHS-Globally Harmonized System of Classification and Labelling of Chemicals with LD₅₀ in mg/kg (UN 2005). The RC
- millimole regression is $\log LD_{50}$ (mmol/kg) = $\log IC_{50}$ (mM) X 0.435 + 0.625. Numbers in table represent number of substances.
- ²Reference rodent LD₅₀ values from Table 4-2 of the BRD.
- ³Carbon tetrachloride excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀.
- ⁴Methanol excluded because no laboratory attained sufficient toxicity for the calculation of an IC₅₀.